Remarks

Applicants have amended claims 37 and 38 to perfect the antecedent basis for certain terms as shown in the Listing of Claims. Amendments are clerical, and thus, do not introduce new matter. The entry of the amendments is respectfully requested.

Applicants now turn to the specific rejections.

The Examiner rejected claim 37 as allegedly not complying with 35 U.S.C. §112, second paragraph, definiteness requirement. Specifically, the Examiner noted that there was insufficient antecedent basis for "the non-replicating vector encoding the prodrug activating enzyme" in line 4 of the claim. The Examiner further noted that there was insufficient antecedent basis for "the replicating vector encoding the apoptosis inhibiting agent" on lines 5-6 of the claim

In view of the amendments to claim 37, Applicants respectfully submit that the rejection has been obviated.

There being no prior art rejections to claim 37, Applicants respectfully submit that claim 37 is in condition for allowance.

The Examiner rejected claims 1, 3-13, and 38 under 35 U.S.C. §103(a) as allegedly being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) for the same reasons already set forth in the Office action mailed on 8/8/07 (pages 6-10). Specifically, the Examiner contended that the

> "...combined teachings of Waxman et al and Bilbao et al ... **do not exclude** the use of an apoptotic factor such as an expression factor [sic] encoding p53 and/or a death receptor ligand Trail under control of a regulatable promoter; and they are not contradictory in any way to the goal to cancer treatment." (Page 8, second full par. of Office Action dated 4/23/08, emphasis original)

The Examiner's statement ignores the teaching of the references and the Declaration of Dr. David Waxman. Not only is Dr. Waxman an expert in this field, but he is also a co-author of the cited Waxman reference and a co-applicant.

The Examiner is essentially ignoring the Declaration by the conclusory statement that the Declaration is not persuasive. Dr. Waxman discussed what the state of the art of cancer treatment was at the time the application was filed (Declaration by Dr. David Waxman filed on 11/8/07 hereinafter referred to as "Waxman"). Dr. Waxman explained that using an apoptosis **inhibiting** agent **in connection with cancer therapy would have gone against the conventional wisdom** of cancer therapeutics at the time the application was filed (par. 13-17 of Waxman Declaration). Namely, the goal of cancer treatment is to kill the cancer cells. Apoptosis is programmed cell death. Thus, to kill the cancer cell you want to **induce** apoptosis, **not inhibit**, apoptosis. Accordingly, the Waxman reference specifically, and based on scientific reasoning, did not include apoptosis **inhibiting** agents. In contrast, the present invention teaches the use of apoptosis inhibiting agents. The combination of Waxman with Bilbao simply does not overcome the essential deficiency of Waxman. Bilbao, Robertson and Beidler are not directed to cancer treatment. Thus, the skilled artisan would not have any basis for combining them. Even if they did, they would have followed Waxman's teaching of using an apoptosis **inducing** agent. Thus, Waxman explained the **scientific basis for omitting the apoptosis inhibiting agents** from the list of agents used in Waxman.

In addition, the Examiner contends that the Applicants attack the cited references individually (page 8, first full par. of 4/23/08 Office Action). Moreover, without any comments to counter the expert testimony in the Waxman Declaration, the Examiner also contended that "an ordinary skilled artisan would have been motivated to modify the teachings of Waxman et al. by further combining the step of transducing neoplastic cells…" (page 8, last full par.).

Applicants are not attacking the references individually. Applicants have given a specific, scientifically based reason **why a skilled artisan would not have been motivated to combine** the cited references. The claims are directed to methods of treating cancer. According to the conventional wisdom in the field of cancer treatment, **a skilled artisan would not apply agents that would appear to result in decreased apoptosis to cancer patients** in whom inducing cell death is the usual goal (see e.g. pars. 13-15 of Declaration of Dr. David Waxman filed on 11/8/07). Moreover, a skilled artisan not having read the present application, would not have had a reasonable expectation of success of treating cancer with a treatment method that

proposed using cell death inhibitors because **use of such agents would have been expected to increase cancer growth, not decrease it**. Thus, contrary to the Examiner's contention that the combination of the references **does not exclude** use of anti-apoptotic agents, the general knowledge in the art or cancer treatment was such that **using anti-apoptotic agents in cancer treatment methods was not even in the realm of possibilities contemplated by a skilled artisan** prior to the filing of the present application.

The Examiner also cited Luo and Wilson. However, the Examiner only states that Luo taught a method in which coexpression of p35 enhanced the inhibition of neointimal formation by Fas ligand via the utilization of Ad2/FasL/p35. Thus, there is nothing in Luo that would provide motivation for a skilled artisan to **use p35 for cancer treatment.** Also Wilson only describes a method for gene transfer comprising the step of exposing a population of host cells in both *in vitro* and in a mammalian patient (e.g., hepatocytes, lung, muscle, epithelial cells) to a recombinant viral vector, which comprises a gene encoding an anti-apoptotic agent (e.g., Bcl-2) and a transgene (e.g., a transgene encoding a growth hormone, erythropoietin, factor IX, or liver enzymes such as ornithine transcarbamylase, arginase and others). **None of the cells used in Wilson were cancer cells**. Thus, there is nothing also in Wilson that would provide motivation for a skilled artisan to use an apoptosis-inhibitor, such as Bcl-2 **for cancer treatment**, wherein, according to the skilled artisans at the time of the filing, **one wanted to induce, not inhibit apoptosis**.

Although Bilbao **shows** that Bcl2 can prolong transgene expression **in normal cells**, Bilbao does **not show** that Bcl2 or any other anti-apoptotic factors can do so **in cancer cells**. Indeed, as already discussed in the declaration by Dr. Waxman, at the time of the present invention, there was the expectation that anti-apoptotic factors would **not** be effective in prolonging transgene expression in cancer cells, insofar as cancer cells already express high levels of anti-apoptotic factors, such as Bcl2. Therefore, one would have been led away from combining Bilbao with Waxman.

Moreover, it was unexpected that tumor cells expressing the prodrug-activating P450 enzyme together with an anti-apoptotic factor would eventually die following prodrug treatment, insofar as the active form of the P450 prodrug was known to kill cancer cells by an apoptotic

mechanism. This unexpected finding indicates that the activated prodrug is eventually able to circumvent the anti-apoptotic factor and kill the cancer cells by a slower, alterative (i.e., a non-apoptotic) mechanism.

Applicants respectfully submit that the Examiner's comment (p. 6, lines 5-7) that Bilbao et al taught that "at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach (page 2, lines 15-27)" is taken out of context. Bilbao made this statement in the context of background information about gene therapy. However, Bilbao does not state, or even imply, that Bcl2 may be useful in enhancing toxin gene therapy for cancer cell treatment.

Further supporting Dr. Waxman's Declaration, Applicants submit herewith two review articles (Exhibits A and B) as examples that specifically support the arguments made by Dr. Waxman regarding the state of the art of the role of apoptosis in cancer. Both of these, and numerous other articles all conclude that lack of apoptosis is a severe problem in cancer. Thus, as already stated by Dr. Waxman, no one in their right mind would have thought of exacerbating the problem by promoting even more lack of apoptosis to treat cancer.

In view of the above, Applicants submit that the rejection of claims 1, 3-13, and 38 under 35 U.S.C. 103(a) over Waxman in view of Bilbao is improper and should be withdrawn.

The Examiner rejected claims 14-18 and 31-33 under 35 U.S.C. 103(a) as allegedly being unpatentable over Waxman in view of Bilbao and further in view of Robertson and Griffith.

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

The combination of Waxman and Bilbao has been discussed above. The addition of Robertson and Griffith fails to provide the missing motivation to combine Waxman with Bilbao.

All Robertson described is the use of a recombinant viral vector expressing various anti-apoptotic polypeptides such as NAIP, HIAP, HIAP2, XIAP and other under the control of a regulatable promoter to inhibit death of a cell of the nervous system in a patient. Griffith only taught a method of **inducing tumor cell apoptosis** using Trail/Apo2-L gene transfer in a mammal, and optionally in combination with chemotherapeutic agents, radiotherapeutic agents

or immune potentiating genes or proteins. Thus, even Griffith provides support for the state of the art declaration by Dr. Waxman in describing that they **used tumor cell apoptosis inducing**, not **inhibiting** agents.

Therefore, contrary to the Examiner's argument, there was nothing in these two references that would have taught a skilled artisan to use the cancer treatment method as claimed.

In view of the above, Applicants submit that the rejection of claims 14-18 and 31-33 under 35 U.S.C. 103(a) over Waxman in view of Bilbao and further in view of Robertson and/or Griffith is improper and should be withdrawn.

The Examiner further rejected claims 1 and 3-6 (with respect to the elected species p35) under 35 U.S.C. 103(a) as being unpatentable over Waxman in view of Bilbao, and further in view of Beidler for the same reasons already set forth in the Office action mailed on 8/8/07.

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

The combination of Waxman and Bilbao has been discussed above. Neither Robertson nor Griffith provide the missing motivation to combine Waxman with Bilbao.

All Beidler described is that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery because p35 inhibits TNF- and Fas-induced apoptosis, blocks the cleavage of PARP, a death substrate in the apoptotic pathway as well as blocking developmental, viral, and x-irradiation-induced cell death. There is no mention in Beidler that p35, or any other anti-apoptotic molecule would be useful for the treatment of cancer.

Therefore, contrary to the Examiner's argument, there was nothing in Beidler that would have taught a skilled artisan to use the cancer treatment method as claimed.

In view of the above, Applicants submit that the rejection of claims 1 and 3-6 under 35 U.S.C. 103(a) over Waxman in view of Bilbao and further in view of Beidler is improper and should be withdrawn.

In view of the foregoing amendments, arguments and evidence, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

The Applicants believe no fees are due at this time. However, in the event that any additional fees are required, the Commissioner is authorized to charge Nixon Peabody LLP Deposit Account No. 50-0850.

Date: October 20, 2008

Respectfully submitted,

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